Bibliographic Cite	Literature Type	Level of Evidence (AMSTAR-2)	Purpose	Population	Intervention and Outcome Measures	Results/ Recommendations	Study Limitations
Alons IM, Jellema K, Wermer MJ, et al. D-dimer for the exclusion of cerebral venous thrombosis: a meta-analysis of low risk patients with isolated headache. BMC Neurol. 2015;15:118.	meta-analysis	Low level of evidence	To determine whether D-dimer may play the same role in low risk CVT patients with isolated headache.	Included were original articles focusing on D-dimer determination in consecutive patients with suspected CVT, where the presence of isolated headache could be determined. Articles were excluded from the meta-analysis if they were reviews or comments. A total of 636 consecutive patients were collected from the authors' data and the literature search.	Of 45 CVT patients one had a negative D-dimer (7.5 %). Sensitivity of D-dimer for diagnosing CVT was 97.8 % (95 % CI: 88.2-99.6 %), specificity was 84.9 % (95 % CI: 81.8-87.7 %), positive predictive value was 33.1 % (95 % CI: 25.2-41.7 %), negative predictive value was 99.8 % (95 % CI: 98.9-100 %). Another 56 isolated headache CVT patients were identified in literature, lacking consecutive isolated headache controls. Sensitivity of D-dimer for diagnosing CVT including these patients was 87.1 % (95 % CI: 79.0-93.0 %).	D-dimers have a high negative predictive value in patients with isolated headache for excluding CVT. Sensitivity is lower but comparable to the values accepted in PE and DVT. Low risk patients were defined as headache patients with a normal neurological examination, normal standard head CT and absence of risk factors such as pregnancy or puerperium. Normal D-dimers in these patients may reduce unnecessary imaging, making it a potential valuable marker.	Risk of bias - one or more key results were based on studies with a majority having a high risk of bias. There was insufficient data on isolated headache and concomitant D-dimer levels in the authors' own data and the literature. Very low risk patients may have been missed compromising the generalizability of the findings.
Georgakis MK, Duering M, Wardlaw JM, et al. WMH and long-term outcomes in ischemic stroke: A systematic review and meta-analysis. Neurology. 2019; 92(12):e1298-e1308.	systematic review and meta-analysis	Moderate level of evidence	To investigate the relationship between baseline white matter hyperintensities (WMH) in patients with ischemic stroke and long-term risk of dementia, functional impairment, recurrent stroke, and mortality.	All prospective or retrospective cohort studies that included patients with ischemic stroke and examining the association of WMH at baseline with the outcomes of interest over a follow-up period of ≥ 3 months. Case–control studies, cross-sectional studies, case reports, case series of < 50 patients, and animal studies were excluded. Target population was adult (≥ 18 years) patients with ischemic stroke. Studies examining exclusively patients with hemorrhagic stroke and patients with TIA were excluded. A total of 104 studies with 71,298 ischemic stroke patients were included.	Authors systematically searched Medline and Scopus for cohort studies of ischemic stroke patients examining whether MRI- or CT-assessed WMH at baseline are associated with dementia, functional impairment, recurrent stroke, and mortality at 3 months or later poststroke. Authors extracted data and evaluated study quality with the Newcastle–Ottawa scale. They pooled relative risks (RR) for the presence and severity of WMH using random effects models.	Moderate/severe WMH at baseline were associated with increased risk of dementia (RR 2.17, 95% confidence interval [CI] 1.72–2.73), cognitive impairment (RR 2.29, 95% CI 1.48–3.54), functional impairment (RR 2.21, 95% CI 1.83–2.67), any recurrent stroke (RR 1.65, 95% CI 1.36–2.01), recurrent ischemic stroke (RR 1.90, 95% CI 1.26–2.88), all-cause mortality (RR 1.72, 95% CI 1.47–2.01), and cardiovascular mortality (RR 2.02, 95% CI 1.44–2.83). The associations followed dose response patterns for WMH severity and were consistent for both MRI- and CT-defined WMH. The results remained stable in sensitivity analyses adjusting for age, stroke severity, and cardiovascular risk factors, in analyses of studies scoring high in quality, and in analyses adjusted for publication bias. The authors conclude that presence and severity of WMH are associated with substantially increased risk of dementia, functional impairment, stroke recurrence, and mortality after ischemic stroke. WMH may aid clinical prognostication and the planning of future clinical trials.	First, the main analyses revealed substantial heterogeneity. Potential sources of this heterogeneity include between-study differences in target population, study design, assessment and quantification of WMH, definition and ascertainment of outcomes, follow-up duration, and statistical approaches. Second, the majority of studies were of rather lower quality. Several of the included studies were not representative of the general stroke population, showed high attrition rates, did not assess whether outcomes were present before stroke, and did not adjust for major confounders such as age, NIHSS, and cardiovascular risk factors. Third, the analyses suggest marked publication bias for all outcomes investigated. However, the associations between WMH and long-term outcomes remained when adjusting for publication bias. Finally, the authors could not examine the influence of the index infarct on the technical assessment of WMH and whether this affected the results.
Kauw F, Takx RA, de Jong HW, et al. Clinical and imaging predictors of recurrent ischemic stroke: A systematic review and meta-analysis. Cerebrovasc Dis. 2018; 45(5-6):279-287.	systematic review and meta-analysis	Moderate level of evidence	To identify clinical and radiological factors for predicting recurrent ischemic stroke in patients with recent ischemic stroke.	10 studies were included for meta-analysis including 6 prospective cohort and 4 retrospective cohort studies. The included studies investigated a total of 212,864 patients with ischemic stroke. Included were studies with unselected population of patients with acute ischemic stroke, outcome of recurrent ischemic stroke and, effect estimate (risk ratio [RR], OR or hazard ratio [HR]) including 95% CI reported or could be calculated. Animal studies, studies in languages other than English, Dutch, German, French, or Spanish, case series, reviews, conference abstracts, and editorials were excluded.	A systematic search in PubMed, Embase, Cochrane Library, and CINAHL was performed with the terms “ischemic stroke,” “predictors/determinants,” and “recurrence.” Quality assessment of the articles was performed and the level of evidence was graded for the articles included for the metaanalysis. Pooled risk ratios (RR) and heterogeneity (I2) were calculated using inverse variance random effects models.	Past medical history of stroke or TIA was a predictor of recurrent ischemic stroke (pooled RR 2.5, 95% CI 2.1–3.1). Small vessel strokes were associated with lower risk of recurrence than large vessel strokes (pooled RR 0.3, 95% CI 0.1–0.7). Patients with stroke of undetermined cause had lower risk of recurrence than patients with large artery atherosclerosis (pooled RR 0.5, 95% CI 0.2–1.1). No studies using CT or ultrasound for prediction of recurrent ischemic stroke were found. The following MRI findings were predictors of recurrent ischemic stroke: multiple lesions (pooled RR 1.7, 95% CI 1.5–2.0), multiple stage lesions (pooled RR 4.1, 95% CI 3.1–5.5), multiple territory lesions (pooled RR 2.9, 95% CI 2.0–4.2), chronic infarcts (pooled RR 1.5, 95% CI 1.2–1.9), and isolated cortical lesions (pooled RR 2.2, 95% CI 1.5–3.2). The authors conclude that, in patients with a recent ischemic stroke, a history of stroke or TIA and the subtype large artery atherosclerosis are associated with an increased risk of recurrent ischemic stroke. Predictors evaluated with MRI include multiple ischemic changes and isolated cortical lesions. Predictors of recurrent ischemic stroke concerning CT or ultrasound have not been published.	A drawback of this study was the possible existence of publication bias. Studies that did not find significant estimates may have been averted from publication. The authors could not formally test publication bias because the amount of studies was too low. No funnel plots were generated, since they may not detect publication bias as less than 10 studies were available per category. Heterogeneity between studies may have been an issue, because differences were present across studies with respect to number of study participants, follow-up durations, and definitions of predictors. Furthermore, patients may have been treated differently across studies because treatment protocols have been improved over the years.
Ryu WHA, Avery MB, Dharampal N, et al. Utility of perfusion imaging in acute stroke treatment: a systematic review and meta-analysis. J Neurointerv Surg. 2017;9(10):1012-6.	systematic review and meta-analysis	Moderate level of evidence	To evaluate the available scientific evidence regarding the utility of perfusion imaging in determining treatment eligibility in patients with acute stroke and in predicting their clinical outcome.	Included were studies that involved perfusion imaging related to AIS management. The interventions of interest were multimodal CT scan and MRI performed as a part of stroke assessment for the adult population. The review included randomized controlled trials, cohort studies, and case-control studies. Excluded were case reports, editorials, technical reports, conference abstracts, and books. Ultimately, 3881 patients in 13 studies were included.	The authors’ literature search yielded 13 studies that met the authors’ inclusion criteria. In total, 994 patients were treated with the aid of perfusion imaging compared with 1819 patients treated with standard care. In the intervention group 51.1% of patients had a favorable outcome at 3 months compared with 45.6% of patients in the control group (p=0.06). Subgroup analysis of studies that used multimodal therapy (IV tissue plasminogen activator, endovascular thrombectomy) showed a significant benefit of perfusion imaging (OR 1.89, 95% CI 1.43 to 2.51, p<0.01).	Perfusion imaging may represent a complementary tool to standard radiographic assessment in enhancing patient selection for reperfusion therapy, with a subset of patients having up to 1.9 times the odds of achieving independent functional status at 3 months. This is particularly important as patients selected based on perfusion status often included individuals who did not meet the current treatment eligibility criteria.	This study has a number of limitations. Given the nature of the systematic review, there is variability in the methodology of included studies such as treatment protocol, imaging processing, and measures of perfusion status. Future research in clarifying and standardizing perfusion imaging techniques will be important to allow broader generalizability of published reports. Another limitation is that only a subset of studies in our systematic review was included in the meta-analysis. The inclusion criteria for the meta-analysis were defined a priori to promote homogeneity in the data for analysis.

Xu W, Gao L, Li T, et al. The performance of CT versus MRI in the differential diagnosis of cerebral venous thrombosis. Thromb Haemost. 2018; 118(6):1067-1077.	meta-analysis	Low level of evidence	To assess the accuracy of CT and MRI in the differential diagnosis of CVT and cerebral venous sinus thrombosis.	Twenty-four eligible articles comprising 48 studies (4,595 cases) were included. Inclusion criteria were: (1) CT and/or MRI used in differential diagnosis of CVT or cerebral sinus thrombosis. (2) No unified 'gold standard' for diagnosis of CVT, so authors chose MRV and/or CTV and/or digital subtraction angiography (DSA) as standard reference. (3) Minimum number of patients included in each study was 10. (4) Sensitivity and/or specificity could be calculated from each study. (5) No overlapping subjects across publications. Different parameters about the same case were treated as different cases for comprehensively evaluating the performance of CT or MRI. (6) Language of eligible studies was either in Chinese or English. The exclusion criteria were: (1) study did not meet inclusion criteria; and (2) reviews, editorials, clinical conference, abstracts, case reports, comment and congresses.	A comprehensive search of the PubMed, EMBASE, Web of Science, Cochrane Database and Chinese Biomedical (CBM) databases was conducted. The data extracted from the enrolled studies were evaluated independently by two of the reviewers. The authors assessed the methodological quality of each article individually and perform a meta-analysis to obtain the summary of the diagnostic accuracy of CT and MRI in correctly identifying CVT and CVST.	The pooled sensitivity for CT–CVT/CT–CVST groups is 0.79 (95% confidence interval [CI]: 0.76, 0.82)/0.81(95% CI: 0.78, 0.84), and pooled specificity is 0.90 (95% CI: 0.89, 0.91)/0.89 (0.88, 0.91), with an area under the curve (AUC) for the summary receiver operating characteristic (SROC) of 0.9314/0.9161, respectively. No significant heterogeneity and publication bias was observed across each study. For MRI–CVT/MRI–CVST, the pooled sensitivity is 0.82 (95% CI: 0.78, 0.85)/0.80 (95% CI: 0.76, 0.83), and pooled specificity is 0.92 (95% CI: 0.91, 0.94)/0.91(0.89, 0.92), with an AUC for the SROC of 0.9221/0.9273, respectively. The authors conclude that the meta-analysis indicates that both CT and MRI have a high level of diagnostic accuracy in the differential diagnosis of CVT and CVST, independent of stage, target for analysis or analysis methods. They could be chosen as alternative suboptimal gold standards for diagnosing CVT and CVST, especially in emergency.	There were several limitations identified. First, there was significant heterogeneity observed in the MRI–CVST group. The meta-regression demonstrated that study design across each study may contribute to the heterogeneity. Although no severe heterogeneity existed in other groups (CT–CVT, CT–CVST, MRI–CVT groups), the included studies varied in study design, reference standard, analysis methods, parameters and its cut-off value and sample sizes, which would potentially increase the clinical heterogeneity. Second, although 48 studies with 4,595 cases were included, there was still limited data for sub-group analysis of different characteristics, such as sub-acute or chronic stage separately for CT and MRI when using different sequences (fluid-attenuated inversion recovery [FLAIR], DWI). More studies were required to incorporate other sub-groups into comparison. Third, only English and Chinese published paperswith full text were enrolled in this meta-analysis, which may leave out some eligible studies that were unpublished or reported in other languages, indicating potential existence of public bias.